Synthesis of some 5*H*,12*H*-[1]Benzoxepino[4,3-*b*]indol-6-ones. A New Heterocyclic Ring System

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The synthesis of the title compounds 5*H*,12*H*-[1]benzoxepino[4,3-*b*]indol-6-ones **10** was effected by the Fischer indole cyclization of some 2,3-dihydro-4-phenylhydrazono[1]benzoxepin-5-ones **9**, obtained from the 3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-ones **7** by the Japp-Klingemann reaction. The structure of these new heterocyclic compounds was supported by ir, ^{1}H nmr and ms spectral data.

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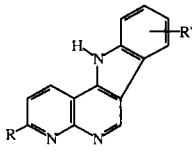
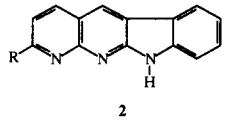
Some years ago, in the course of our work on the synthesis of new heteropolycyclic compounds, we have described numerous 11*H*-indolo[3,2-*c*][1,8]naphthyridines **1** [1] and some 6*H*-indolo[2,3-*b*][1,8]naphthyridines **2** [2], with potential antitumor properties. More recently, a number of 5,7-dihydro-5-oxopyrido[3′,2′:5,6]pyrimido[1,2-*a*]benzimidazoles **3** [3] and 5,11-dihydro-5-oxopyrido[2′,3′:4,5]-pyrimido[1,2-*a*]benzimidazoles **4** [4], as potential antitumor agents, were synthesized in our laboratory. Compounds **1**, **2** and **3** contain a new heterocyclic ring system.

Pursuing our interest in heteropolycyclic compounds, in particular in the field of indole derivatives which might exhibit pharmacological activity because of their structural resemblance to some very important alkaloids as strychnine, reserpine, ellipticine *etc.*, we wish to report here an high-yield synthesis of some 5*H*,12*H*-[1]benzoxepino-[4,3-*b*]indol-6-one derivatives **10**, which represent a new heterocyclic ring system. To the best of our knowledge, only one report on an analogous isomeric ring system, the 1*H*-[2]benzoxepino[4,3-*b*]indole **5**, is found in the literature [5].



1



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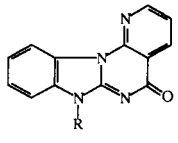

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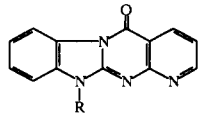

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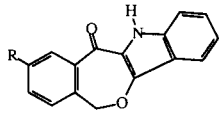

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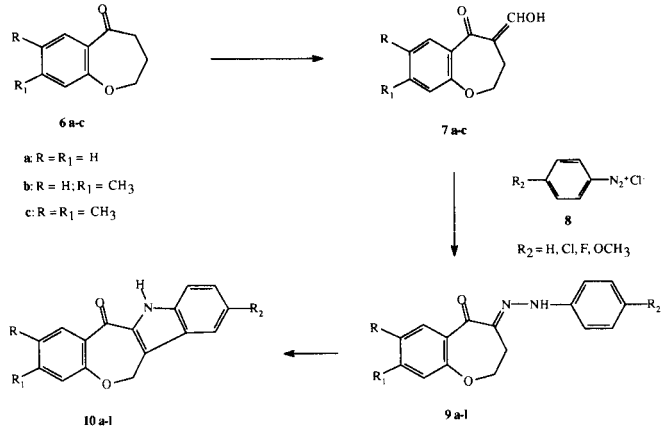
The title compounds **10** were synthesized as shown in Scheme 1. The preparation of the starting 3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-ones **7a** and **7b** has already been described [6]. The unknown dimethyl compound **7c** was prepared in similar manner, from ketone **6c**, by reaction with ethyl formate in anhydrous benzene in the presence of sodium methoxide. The target compounds 5*H*,12*H*-[1]benzoxepino[4,3-*b*]indol-6-ones **10** were synthesized using the Fisher indole synthesis on the appropriate phenylhydrazones **9**, obtained from the 3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-ones **7** by the Japp-Klingemann reaction [7]. This reaction, where a diazonium salt couples with a compound containing a methine active group, was particularly convenient to obtain the phenylhydrazones **9**. They can be directly converted to derivatives **10**, without previous purification, by reflux in hydrogen chloride ethanolic solution, with yields ranging between 75% to 98%.

Scheme 1



The physical and spectral data of compounds **9** and **10** are reported in Tables 1 and 2, 3 and 4, respectively. The structures of all new compounds were confirmed by analytical and ir, ^{1}H nmr and ms data.

Table 1

Physical Data for Compounds **9a-l**

Compound No.	R	R_1	R_2	Yield (%)	Mp (°C) (recrystallization solvent)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
9a	H	H	H	75	102-103 (methanol)	$C_{16}H_{14}N_2O_2$	72.18 72.17	5.26 5.33	10.53 10.61
9b	H	H	Cl	93	111-112 (methanol)	$C_{16}H_{13}N_2O_2Cl$	63.89 63.90	4.33 4.25	9.32 9.10
9c	H	H	F	98	112-113 (methanol)	$C_{16}H_{13}N_2O_2F$	67.61 67.50	4.58 4.63	9.86 9.86
9d	H	H	OCH_3	64	97-98 (methanol)	$C_{17}H_{16}N_2O_3$	68.92 68.80	5.40 5.30	9.46 9.55
9e	CH_3	H	H	54	124-126 (methanol)	$C_{17}H_{16}N_2O_2$	72.86 72.70	5.71 5.65	10.00 9.89
9f	CH_3	H	Cl	89	137-138 (methanol)	$C_{17}H_{15}N_2O_2Cl$	64.86 64.70	4.77 4.77	8.90 8.75
9g	CH_3	H	F	78	121-122 (methanol)	$C_{17}H_{15}N_2O_2F$	68.46 68.44	5.03 5.15	9.40 9.20
9h	CH_3	H	OCH_3	75	95-96 (methanol)	$C_{18}H_{18}N_2O_3$	69.68 69.81	5.81 6.01	9.03 8.90
9i	CH_3	CH_3	H	84	106-107 (methanol)	$C_{18}H_{18}N_2O_2$	73.47 73.30	6.12 6.24	9.52 9.35
9j	CH_3	CH_3	Cl	67	155-157 (methanol)	$C_{18}H_{17}N_2O_2Cl$	65.75 65.77	5.17 5.25	8.52 8.45
9k	CH_3	CH_3	F	72	132-134 (methanol)	$C_{18}H_{17}N_2O_2F$	69.23 69.01	5.45 5.46	8.97 8.75
9l	CH_3	CH_3	OCH_3	64	115-116 (methanol)	$C_{19}H_{20}N_2O_3$	70.37 70.17	6.17 6.27	8.64 8.44

EXPERIMENTAL

Melting points were determined using a Reichert Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a PYE/UNICAM Model PU 9561 spectrophotometer in Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian EM 360 A or a Bruker AC 200 spectrometers using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc was carried out on Merck 0.25 mm precoated silica gel glass plates (60 F-254). Elemental analyses were performed by our Analytical Laboratory and agreed with theoretical values to within ±0.4%.

7,8-Dimethyl-3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-one **7c**.

A solution of ethyl formate (5.5 g, 74 mmoles) in dry benzene (15 ml) was added dropwise to a suspension of freshly prepared sodium methoxide (4.0 g, 74 mmoles) in the same solvent (15 ml). The ice-cooled mixture was treated dropwise with stirring, under dry nitrogen, with a solution of 7,8-dimethyl-3,4-dihydro[1]benzoxepin-5(2*H*)-one **6c** (7.0 g, 37 mmoles) in dry benzene (20 ml). Stirring was continued at room temperature for 20 hours. The sodium salt of **7c**, as a yellow precipitate, was collected and dissolved in a small amount of water. The solution was acidified at 0° with hydrochloric acid to give **7c** (2.8 g, yield 61%). An analytical sample was obtained by recrystallization from petroleum ether 40-60°, mp 80-81°; ir: 1620 (C=O), 1590 (C=C) cm^{-1}; ^1H nmr (deuteriochloroform): 2.23 (s, 6H, 7- and 8-CH_3), 2.58 (t, 2H, 3-CH_2), 4.30 (t, 2H, 2-CH_2), 4.57 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 8.40 (s, 1H, 4-CH) ppm; ms: m/z (relative intensity) 218 (M^+ 60), 29 (100).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.40; H, 6.60.

General Procedure for the Preparation of 2,3-Dihydro-4-phenylhydrazono[1]benzoxepin-5-ones **9a-l**.

A solution of 25 mmoles of **7a-c** in 20 ml of methanol was added to an aqueous saturated solution of 75 mmoles of sodium acetate trihydrate. After cooling at 0°, a solution of the suitable diazonium salt **8**, obtained from the appropriately substituted aniline in dilute hydrochloric acid and sodium nitrite, was added dropwise in slight excess. A yellow-orange precipitate is immediately formed. The mixture was stirred for half an hour at 0° and at room temperature for 3 hours. The solid was collected and washed with water. It can be directly used in the Fisher indole synthesis.

Table 2

IR and NMR Spectral Data of Compounds **9a-l**

Compound No.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
9a	1600, 1520, 1210, 1170, 1100, 1000	2.80-3.13 (m, 2H, 3-CH_2), 4.47 (t, 2H, 2-CH_2), 7.08-8.00 (m, 9H, Ar-H), 10.07 (s, 1H, Ph-NH) [a]
9b	1590, 1570, 1500, 1250, 990, 760	2.91 (t, 2H, 3-CH_2), 4.45 (t, 2H, 2-CH_2), 7.06-7.78 (m, 8H, Ar-H) [b]
9c	1620, 1600, 1520, 1200, 1000, 840	2.80-3.31 (m, 2H, 3-CH_2), 4.48 (t, 2H, 2-CH_2), 7.00-8.00 (m, 8H, Ar-H), 10.10 (s, 1H, Ph-NH) [a]
9d	1600, 1500, 1230, 1190, 1150, 980	2.77-3.01 (m, 2H, 3-CH_2), 3.77 (s, 3H, 4'-OCH_3), 4.46 (t, 2H, 2-CH_2), 6.87-8.03 (m, 8H, Ar-H), 10.00 (s, 1H, Ph-NH) [a]
9e	1600, 1580, 1520, 1160, 1030, 760	2.33 (s, 3H, 7-CH_3), 2.67-3.10 (m, 2H, 3-CH_2), 4.38 (t, 2H, 2-CH_2), 6.87-7.87 (m, 8H, Ar-H), 10.07 (s, 1H, Ph-NH) [a]
9f	1630, 1600, 1580, 1150, 1020, 820	2.33 (s, 3H, 7-CH_3), 2.75-3.13 (m, 2H, 3-CH_2), 4.43 (t, 2H, 2-CH_2), 6.90-7.67 (m, 7H, Ar-H), 10.16 (s, 1H, Ph-NH) [a]
9g	1620, 1590, 1270, 1020, 880, 830	2.33 (s, 3H, 7-CH_3), 2.73-3.10 (m, 2H, 3-CH_2), 4.38 (t, 2H, 2-CH_2), 6.90-7.67 (m, 7H, Ar-H), 10.06 (s, 1H, Ph-NH) [a]
9h	1590, 1530, 1510, 1160, 1040, 830	2.36 (s, 3H, 7-CH_3), 2.86 (t, 2H, 3-CH_2), 3.81 (s, 3H, 4'-OCH_3), 4.41 (t, 2H, 2-CH_2), 6.86-7.52 (m, 7H, Ar-H) [b]
9i	1620, 1590, 1220, 1130, 940, 830	2.13 (s, 6H, 7- and 8-CH_3), 2.67-3.03 (m, 2H, 3-CH_2), 4.36 (t, 2H, 2-CH_2), 6.83-7.60 (m, 7H, Ar-H), 9.97 (s, 1H, Ph-NH) [a]
9j	1600, 1580, 1520, 1240, 1200, 830	2.17 (s, 6H, 7- and 8-CH_3), 2.67-3.03 (m, 2H, 3-CH_2), 4.37 (t, 2H, 2-CH_2), 6.93-7.63 (m, 6H, Ar-H), 10.10 (s, 1H, Ph-NH) [a]
9k	1620, 1560, 1180. 1140. 950, 820	2.26 and 2.28 (two s, 6H, for 7- and 8-CH_3), 2.89 (t, 2H, 3-CH_2), 4.40 (t, 2H, 2-CH_2), 6.84-7.52 (m, 6H, Ar-H) [b]
9l	1610, 1580, 1300, 1190, 1040, 830	2.27 (s, 6H, 7 and 8-CH_3), 2.73-3.10 (m, 2H, 3-CH_2), 3.77 (s, 3H, 4'-OCH_3), 4.38 (t, 2H, 2-CH_2), 6.83-7.63 (m, 6H, Ar-H), 9.87 (s, 1H, Ph-NH) [a]

[a] Recorded on a Varian EM 360 A in dimethyl sulfoxide-d_6 (DMSO-d_6). [b] Recorded on a Bruker AC 200 in deuteriochloroform ($CDCl_3$).

Table 3

Physical Data of Compounds **10a-l**

Compound No.	R	R_1	R_2	Yield (%)	Mp (°C) (recrystallization solvent)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
10a	H	H	H	95	226-227 (benzene)	$C_{16}H_{11}NO_2$	77.11 76.99	4.42 4.34	5.62 5.54
10b	H	H	Cl	81	>300 (DMF)	$C_{16}H_{10}NO_2Cl$	67.72 67.82	3.53 3.63	4.94 4.96
10c	H	H	F	78	270-271 (benzene)	$C_{16}H_{10}NO_2F$	71.91 71.85	3.74 3.72	5.24 5.18
10d	H	H	OCH_3	90	224-225 (benzene)	$C_{17}H_{13}NO_3$	73.12 73.00	4.66 4.67	5.02 5.19
10e	CH_3	H	H	84	223-224 (benzene)	$C_{17}H_{13}NO_2$	77.57 77.67	4.94 5.06	5.32 5.32
10f	CH_3	H	Cl	75	>300 (benzene)	$C_{17}H_{12}NO_2Cl$	68.57 68.47	4.03 3.93	4.71 4.80
10g	CH_3	H	F	86	281-282 (benzene)	$C_{17}H_{12}NO_2F$	72.60 72.65	4.27 4.35	4.98 4.83
10h	CH_3	H	OCH_3	95	248-250 (benzene)	$C_{18}H_{15}NO_3$	73.72 73.82	5.12 5.18	4.78 4.67
10i	CH_3	CH_3	H	80	272-274 (benzene)	$C_{18}H_{15}NO_2$	77.98 78.01	5.41 5.47	5.05 4.95

10j	CH_3	CH_3	Cl	79	>300 (benzene)	$C_{18}H_{14}NO_2Cl$	69.34 69.26	4.49 4.60	4.49 4.39
10k	CH_3	CH_3	F	75	>300 (benzene)	$C_{18}H_{14}NO_2F$	73.22 73.27	4.75 4.75	4.75 4.62
10l	CH_3	CH_3	OCH_3	81	267-269 (benzene)	$C_{19}H_{17}NO_3$	74.27 74.35	5.54 5.58	4.56 4.46

Table 4

IR, NMR and Mass Spectral Data of Compounds **10a-l**

Compound No.	IR (cm^{-1})	^{1}H-NMR (δ ppm) [a]	MS m/z (R.I. %)
10a	3300, 1620, 1600, 1280, 1040, 720	5.48 (*s*, 2H, 12-CH_2), 7.16-8.28 (m, 8H, Ar-H), 9.47 (*s*, 1H, 5-NH)	M+ 249 (53), 220 (100)
10b	3300, 1620, 1600, 1280, 1010, 760	5.43 (*s*, 2H, 12-CH_2), 7.22-8.25 (m, 7H, Ar-H), 9.30 (*s*, 1H, 5-NH)	M+ 283 (68), 254 (100)
10c	3300, 1600, 1580, 1270, 1120, 760	5.43 (*s*, 2H, 12-CH_2), 7.12-8.26 (m, 7H, Ar-H), 9.28 (*s*, 1H, 5-NH)	M+ 267 (58), 238 (100)
10d	3300, 1620, 1590, 1270, 1110, 720	3.88 (*s*, 3H, 2-OCH_3), 5.44 (*s*, 2H, 12-CH_2), 6.99-8.26 (m, 7H, Ar-H), 9.34 (*s*, 1H, 5-NH)	M+ 279 (100)
10e	3300, 1630, 1600, 1340, 1280, 720	2.41 (*s*, 3H, 8-CH_3), 5.45 (*s*, 2H, 12-CH_2), 7.11-8.02 (m, 7H, Ar-H), 9.24 (*s*, 1H, 5-NH)	M+ 263 (62), 234 (100)
10f	3300, 1630, 1600, 1280, 1140, 820	2.41 (*s*, 3H, 8-CH_3), 5.39 (*s*, 2H, 12-CH_2), 7.11-8.10 (m, 6H, Ar-H), 9.28 (*s*, 1H, 5-NH)	M+ 297 (75), 268 (100)
10g	3275, 1630, 1600, 1280, 1130, 820	2.40 (*s*, 3H, 8-CH_3), 5.38 (*s*, 2H, 12-CH_2), 7.11-8.00 (m, 6H, Ar-H), 9.27 (*s*, 1H, 5-NH)	M+ 281 (67), 252 (100)
10h	3300, 1620, 1590, 1270, 1220, 820	2.41 (*s*, 3H, 8-CH_3), 3.88 (*s*, 3H, 2-OCH_3), 5.41 (*s*, 2H, 12-CH_2), 7.05-8.02 (m, 6H, Ar-H), 9.18 (*s*, 1H, 5-NH)	M+293 (100)
10i	3275, 1630, 1600, 1340, 1260, 740	2.31 and 2.32 (two *s*, 6H, for 8- and 9-CH_3), 5.43 (*s*, 2H, 12-CH_2), 7.01-7.98 (m, 6H, Ar-H), 9.37 (*s*, 1H, 5-NH)	M+ 277 (87), 248 (100)
10j	3275, 1630, 1600, 1260, 1120, 800	2.31 and 2.32 (two *s*, 6H, for 8- and 9-CH_3), 5.38 (*s*, 2H, 12-CH_2), 7.01-7.95 (m, 5H, Ar-H), 9.31 (*s*, 1H, 5-NH)	M+ 311 (94), 282 (100)
10k	3300, 1620, 1600, 1260, 1140, 840	2.31 and 2.32 (two *s*, 6H, for 8- and 9-CH_3), 5.36 (*s*, 2H, 12-CH_2), 7.01-7.96 (m, 5H, Ar-H), 9.29 (*s*, 1H, 5-NH)	M+ 295 (86), 266 (100)
10l	3300, 1620, 1600, 1160, 1120, 820	2.31 and 2.32 (two *s*, 6H, for 8- and 9-CH_3), 3.88 (*s*, 3H, 2-OCH_3), 5.39 (*s*, 2H, 12-CH_2), 6.97-7.97 (m, 5H, Ar-H), 9.26 (*s*, 1H, 5-NH)	M+ 307 (100)

[a] Recorded on a Bruker AC 200 in deuteriochloroform ($CDCl_3$).

The recrystallization solvents, yields, analytical, and spectral data for compounds **9a-l** are given in Table 1 and 2.

General Procedure for the Preparation of 5*H*,12*H*-[1]Benzoxepino[4,3-*b*]indol-6-ones **10a-l**.

A solution of 2 mmoles of phenylhydrazone **9** in 10 ml of hydrogen chloride ethanolic solution was refluxed for 10 minutes. After cooling, the yellow-orange precipitate was collected and washed with ethanol.

The recrystallization solvents, yields, analytical and spectral data for compounds **10a-l** are given in Table 3 and 4.

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